Compounds of general formula I as well as their pharmaceutically compatible salts are described, in which R₁ stands for hydrogen, Cₐ₋₅-alkyl, COR, COOR, COSR₂ or CONHR₂, in which R₂ is C₅₋₁₀-alkyl or unsubstituted or substituted aryl and in which R₃ is hydrogen, Cₐ₋₅-alkyl or unsubstituted or substituted aryl, in which R₄ also stands for hydrogen, Cₐ₋₅-alkyl or Cₐ₋₅-acyl, and R₅ stands for a CₙFₙ⁺₂ group, in which n=1, 2, or 3, or a CH₂O(CH₂)ₘCₗFₙ⁺₂ group, in which m=0 or 1 and n=1, 2 or 3. In addition, a process for the production of the compounds with general formula I is indicated. The compounds can be used for the production of pharmaceutical agents.
This applicant claims the benefit of U.S. Provisional Application No. 60/449,401 filed Feb. 25, 2003.

DESCRIPTION

This invention relates to new 17α-fluoroalkyl-11β-benzaldoxime steroids, a process for their production, pharmaceutical preparations that contain these active ingredients as well as their use for the production of pharmaceutical agents, especially for postmenopausal substitution therapy of gynecological diseases, such as hysteromyomas or dysmenorrheic symptoms.

Antigestagenically active steroids are already known from EP 0 057 115 A2. In this connection, this can be 3-oxo-2,4,9-trienes substituted in 11-position.

11β-Benzaldoximes of the steroid series that have special antigestagenic properties are known from DE 43 32 283 A1, DE 43 32 284 A1, and DE 198 09 845 A1 (WO 9945023 A1).

Described in DE 43 32 283 A1 and DE 43 32 284 A1 are 11β-benzaldoxime-3-oxo-2,4,9-diene derivatives, which can be substituted according to DE 43 32 283 A1 in 17β-position with hydroxy, alkoxy, acyloxy or aryloxy and in 17α-position with ω-fluoroalkyl.

In DE 198 09 845 A1, substituted 11β-benzaldoxime-3-oxo-2,4,9-diene is described. In this case, these are S-substituted carboxylic acid thiol esters of these compounds. The compounds can also be substituted in 17β-position with hydroxy, alkoxy, acyloxy or aryloxy and in 17α-position with ω-fluoroalkyl.

By contrast, steroids with 17α-fluoroalkyl chains are disclosed in DE 197 06 061 A1. These compounds, especially ZK 230211 (11β-(4-acycloxyphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one): U. Fuhmann, H. Hess-Stumpf, A. Cleve, G. Neef, W. Schwede, J. Hoffmann, K-H. Fritzemeier and K. Chwalisz (J. Med. Chem., 2000, 43, 5010–5016), show an almost purely antagonistic activity, high receptor selectivity and, i.a., antiproliferative activity in the tumor models.

The object on which this invention is based consists in finding active ingredients with antigestagenic action that have significantly reduced antifluccorticoid action compared to the known compounds and that are suitable for postmenopausal substitution therapy or for treatment of gynecological diseases, such as hysteromyomas or dysmenorrheic symptoms.

Another object on which this invention is based consists in finding a process for the production of active ingredients.

In addition, an object exists in finding pharmaceutical preparations that contain the active ingredients.

The compounds according to the invention have general formula I:

\[ R_1 \text{ stands for hydrogen, } C_1- \text{ to } C_6 \text{-alkyl, COR, COOR, COSR, or CONHR, in which } R_2 \text{ is } C_1- \text{ to } C_6 \text{-alkyl or unsubstituted or substituted aryl, and in which } R_3 \text{ is hydrogen, } C_1- \text{ to } C_6 \text{-alkyl or unsubstituted or substituted aryl,} \]

\[ R_1 \text{ stands for hydrogen, } C_1- \text{ to } C_6 \text{-alkyl or } C_1- \text{ to } C_6 \text{-acyl, and } \]

\[ R_3 \text{ stands for a } C_6 \text{H}_2\text{F}_{2n+1} \text{ group, in which } n=1,2 \text{ or } 3, \text{ or for a } C_6\text{H}_2\text{(CH}_2\text{)}_m\text{C}_6\text{F}_{2n+1} \text{ group, in which } m=0 \text{ or } 1 \text{ and } n=1,2 \text{ or } 3 \]

In all positions of the steroid skeleton as well as on the phenylene radical in 11β-position, any other substituents, especially alkyl and aryl groups, can be bonded instead of hydrogen. In addition, this invention relates to pharmaceutically compatible salts of these compounds. Such acid addition salts can be salts of inorganic and organic acids, for example salts of hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, malic acid, citric acid, salicylic acid, adipic acid and benzoic acid. Other usable acids are described in, for example: Fortschrritte der Arzneimittelforschung [Progress in Pharmaceutical Agent Research], Vol. 10, pages 224–225, Birkhäuser Verlag, Basel and Stuttgart, 1966 as well as in: Journal of Pharmaceutical Sciences, Vol. 66, pages 1–5 (1977).

Radicals \( R_1 \) that are mentioned in this invention are especially a hydrogen atom or a methyl group or acyl groups, such as, for example, formyl, acetyl, propionyl and benzoyl radicals, or carboxylic acid ester groups, for example methoxycarbonyl radicals or ethoxycarbonyl radicals, or carboxylic acid thiol ester groups, such as methylthiocarbonyl radicals or ethylthiocarbonyl radicals, or urethane groups, such as ethylaminocarbonyl radicals or unsubstituted or substituted phenylaminocarbonyl radicals. The substituted phenylaminocarbonyl radical is preferably substituted with a \( C_1- \text{ to } C_6 \text{-fluoroalkyl radical.} \)

\( R_2 \) preferably stands for a hydrogen atom, a methyl group or an acetyl group.

\( R_3 \) stands in particular for a perfluoroalkyl with \( n=1,2 \) or 3. \( R_3 \) can thus stand for 1,1,1-Trifluoromethyl, 1,1,2,2,2-Pentafluoroethyl or 1,1,2,3,3,3-Heptafluoropropyl. In addition, \( R_3 \) can stand for 1,1,1-Trifluoroethoxymethyl, if \( R_3 \) is provided by general formula \( C_6\text{H}_2\text{(CH}_2\text{)}_m\text{C}_6\text{F}_{2n+1} \text{, and in this case, } m=1 \text{ and } n=1 \).

The compounds according to the invention are especially the following 17α-fluoroalkyl-11β-benzaldoxime steroids:

1) \( 4-\text{[17β-Hydroxy-17α-(1,1,1-Trifluoromethyl)]-3-oxoestra-4,9-dien-11β-ylbenzaldehyde}(1-E)-oxime} \)

2) \( 4-\text{[17β-Hydroxy-17α-(1,1,1-Trifluoromethyl)]-3-oxoestra-4,9-dien-11β-ylbenzaldehyde}(1-Z)-oxime} \)
3) 4-[17β-Hydroxy-17α-(1,1,1-trifluoromethyl)-3-oxoestra-4,9-dien-17β-yl]benzaldehyde-1(E)-O-(ethylamino)carbonyl]oxime
4) 4-[17β-Hydroxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-acetyl]oxime
5) 4-[17β-Hydroxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylthio)carbonyl]oxime
6) 4-[17β-Hydroxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethoxy)carbonyl]oxime
7) 4-[17β-Hydroxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylamino)carbonyl]oxime
8) 4-[17β-Hydroxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethoxy)carbonyl]oxime
9) 4-[17β-Hydroxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(methoxy)carbonyl]oxime
10) 4-[17β-Hydroxy-17α-(1,2,2,3,3,3-heptafluoropropyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylamino)carbonyl]oxime
11) 4-[17β-Methoxy-17α-(1,1,1-trifluoromethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylthio)carbonyl]oxime
12) 4-[17β-Methoxy-17α-(1,1,1-trifluoromethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylamino)carbonyl]oxime
13) 4-[17β-Methoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-acetyl]oxime
14) 4-[17β-Methoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethoxy)carbonyl]oxime
15) 4-[17β-Methoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylamino)carbonyl]oxime
16) 4-[17β-Methoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(4'-trifluoromethoxy)phenylamino]carbonyl]oxime
17) 4-[17β-Methoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethoxy)carbonyl]oxime
18) 4-[17β-Methoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(methylthio)carbonyl]oxime
19) 4-[17β-Methoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylthio)carbonyl]oxime
20) 4-[17β-Acetoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylamino)carbonyl]oxime
21) 4-[17β-Acetoxy-17α-(1,2,2,2-pentafluoroethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylamino)carbonyl]oxime
22) 4-[17β-Hydroxy-17α-(1,1,1-trifluoroethoxy) methyl]-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-(ethylthio)carbonyl]oxime

In the prior art documents, the 17α-fluoroalkyl-11β-benzaldehyde sterols and ester, thiol ester or urethane derivatives thereof are not disclosed. The compounds according to the invention are therefore new and not previously known from the literature. The biological profile of action of the above-mentioned compounds is not described. It is not possible to cover all potential applications with an “antigestagen” (W. Elger, K. Chwalisz, Reproduktions-

which are required for the production of the compounds according to the invention with general formula I, is described in EP 0 411 733 A2 and DE 43 32 283 A1:

For the production of the compounds with general formula II, for example, a compound that is indicated with general formula III below can be used, whereby R², R⁴, R⁵, R⁷ and R⁸ have the meaning of corresponding radicals R⁴, R⁵, R⁷ or R⁸ that are indicated in EP 0 411 733 A2 in formula II:
and in this connection, the latter are converted under acid treatment in a water-miscible solvent, optionally while being heated, in a compound in which the radicals are reacted in 3-position to form a 3-oxo group, and a Δ4,5-double bond in the steroid skeleton is formed by release of the hydroxy group in 5α-position. In this connection, more detailed information is contained in EP 0 411 733 A2, which is incorporated herewith in this application as a disclosure. The processes that are used for the production of compounds with general formula III, which depend on the ultimately desired substitutions of the compounds according to the invention, are also indicated in more detail in EP 0 411 733 A2. Therefore, the disclosure that is related thereto in this document is also incorporated in this application. The corresponding data in DE 43 32 283 A1 for the production of compounds with general formula II are also incorporated as disclosures in this application.

To form the benzaldoxide group and thus to produce the compounds of general formula I according to the invention, it is proposed in a way according to the invention to react the compound with general formula II that is obtained by introducing the fluorinated alkyl group in 17β-position with a salt of a hydroxylamine in a basic solvent, such that a 17α-fluoroalkyl-11β-benzaldoxide steroid is produced, in which R₁ is hydrogen, and then optionally to esterify this compound, to etherify it or to convert it into a corresponding carbonate, carboxylic acid derivative or thioacetic acid derivative. The additional radicals R₂ and R₃ in this general formula have the meanings that are further indicated above. The salt of the hydroxylamine in this case is preferably a hydrochloride or hydroxysulfate. The basic solvent is preferably pyridine.

For the production of the compounds according to the invention, the compound with general formula II can be reacted in an entirely different embodiment of the invention also with a compound with general formula NH₂—O—R₁, in which R₁ has the previously-mentioned meaning. Also, in this connection, reference is made to the corresponding description in DE 43 32 283 A1, which is incorporated herewith in the disclosure of this application.

The methods for the in-vitro tests and the in-vivo tests with the compounds according to the invention can be found in EP 0 411 733 A2 and DE 43 32 283 A1:

The 17α-fluoroalkyl-11β-benzaldoxide steroids according to the invention are bonded to the progesterone receptor (cf. Table 1) and in comparison to RU 486 (11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-propinyl-estra-4,9-dien-3-one) generally have a considerably reduced anti-glucocorticoidal action, detected by the reduced glucocorticoid receptor bond in vitro (cf. Table 1).

### TABLE 1

<table>
<thead>
<tr>
<th>Compound according to Example</th>
<th>Relative Molar Binding-affinity RBA (%) to the Progesterone Receptor</th>
<th>Relative Molar Binding-affinity RBA (%) to the Glucocorticoid Receptor Dexamethasone = 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>272</td>
<td>163</td>
</tr>
<tr>
<td>2</td>
<td>123</td>
<td>113</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
<td>187</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>230</td>
<td>84</td>
</tr>
</tbody>
</table>

For comparison:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative Molar Binding-affinity RBA (%)</th>
<th>Relative Molar Binding-affinity RBA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RU 486*</td>
<td>506</td>
<td>685</td>
</tr>
<tr>
<td>Mifepristone*</td>
<td>22</td>
<td>39</td>
</tr>
</tbody>
</table>

*RU 486: 11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-propinyl-estra-4,9-dien-3-one

### TABLE 2

Early Abortive Action in Rats after Subcutaneous Administration from the 5th to 7th Day of Pregnancy (Administration 0.2 ml/

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose (mg/Animal/Day)</th>
<th>Complete Inhibition of Pregnancy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0/6</td>
<td>0</td>
</tr>
<tr>
<td>Example 1</td>
<td>1</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>3/4</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>2/4</td>
</tr>
<tr>
<td>Example 2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Example 3</td>
<td>1</td>
<td>4/4</td>
</tr>
<tr>
<td>Example 4</td>
<td>1</td>
<td>2/4</td>
</tr>
<tr>
<td>Example 6</td>
<td>1</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0/4</td>
</tr>
<tr>
<td>RU 486**</td>
<td>3</td>
<td>5/5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1/5</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>0/5</td>
</tr>
<tr>
<td>ZK 220 211***</td>
<td>3</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3/4</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>0/6</td>
</tr>
</tbody>
</table>

*Empty Uteri
**RU 486: 11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-propinyl-estra-4,9-dien-3-one
***ZK 220 211: 11β-(4-Acetylphenyl)-17β-hydroxy-17α-(1,2,2,2-pentafluoroethoxy)-estra-4,9-dien-3-one
N: Number of paired females
N*: Number of nonpregnant females

The compounds according to the invention are suitable for postmenopausal substitution therapy and for treatment of gynecological diseases, such as hystero-omias, as well as for treatment of dysmenorrheic symptoms.

Subjects of this invention are also pharmaceutical substances (pharmaceutical preparations) for oral, rectal, subcutaneous, intravenous or intramuscular use, which together with commonly used vehicles and optionally diluents contain at least one compound with general formula I as active ingredient.

Pharmaceutical agents according to the invention are produced with commonly used solid or liquid vehicles and/or diluents and the common generally used adjuvants corresponding to the desired type of administration in a suitable dosage and in a way that is known in the art.
preferred oral dispensing form, preferably tablets, films, coated tablets, capsules, pills, powders, solutions or suspensions are also prepared as a depot form.

In addition, parenteral dosage forms, such as injection solutions or else suppositories, are taken into consideration.

Dosage forms as tablets can be produced, for example, by mixing active ingredient with known adjuvants, such as dextrose, sugar, sorbitol, mannitol, polyvinyl pyrrolidone, explosives, such as corn starch or algicn acid, binders, such as starch or gelatin, lubricants, such as magnesium stearate or talc, and/or agents that can achieve a depot effect, such as carboxypolymethylene, carboxymethyl cellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets can also consist of several layers.

Coated tablets analogously can be prepared by coating cores, which are produced analogously to the tablets, with agents that are commonly used in tablet coatings, for example polyvinyl pyrrolidone or shellac, gum arabic, talc, titanium dioxide or sugar. The shell of the coated tablet in this case can also consist of several layers, whereby, for example, the above-mentioned adjuvants are used.

The solutions or suspensions with the active ingredient according to the invention can be mixed for improving the taste with substances, such as saccharine, cyclamate or sugar, and/or with flavoring substances, such as vanilla or orange extract. In addition, they can be mixed with suspension adjuvants, such as sodium carboxymethyl cellulose, or preservatives, such as p-hydroxybenzoic acid.

The capsules can be produced by mixing pharmaceutical substance with vehicles, such as lactose or sorbitol, which then are introduced into the capsules.

Suppositories can preferably be produced by mixing active ingredient with suitable carrier materials, such as neutral fats or polyethylene glycols or derivatives thereof.

The galenical preparation contains the active ingredients in an amount of 1–100 mg, whereby when used in humans, amounts in the range of 1–600 mg per day are required. This explanation is intended, but not limited, by the subsequent examples.

EXAMPLE 1

a) Production of the Starting Compound:

4-[17β-Hydroxy-17α-(1,1,1-trifluoromethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde

1 g of 3,3-dimethoxy-11β-[4-(1,1-ethylenedioxy) methyl]phenyl]-5α-hydroxy-estr-9-en-17-one is dissolved in 30 ml of absolute THF, mixed with 1.0 g of molecular sieve 3A and stirred for 30 minutes under argon. It is cooled to 0°C, 1.5 ml of trifluoromethylmethanesilane is added, it is stirred for 10 more minutes, and the 1 g of tributyl-lammonium fluoride is added. After 10 minutes at 5°C, the reaction solution is decomposed by adding 10 ml of 1N HCl. It is allowed to reach room temperature, in each case 100 ml of water and ethyl acetate are added. The phases are separated, the organic phase is washed neutral, dried on sodium sulfate, the organic phase is filtered off and concentrated by evaporation under vacuum. After acetone is added, 1.05 g of yellow crystals remains. Recrystallization from acetone and treatment with tert-butyl methyl ether yields 480 mg of 4-[17β-hydroxy-17α-(1,1,1-trifluoromethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde. The mother liquor is purified by means of chromatography and yields another 320 mg of aldehyde product.

Melting point: 284–292°C (acetone)

αD = +221° (CHCl3)

1H-NMR: [300 MHz, CDCl3, TMS]: 0.58 (s, 3H, H-18); 4.51 (d, 1H, J=7.1 Hz, H-11α); 5.81 (s, 1H, H-4); 7.38 (d, 2H, J=8.3 Hz, CH-arom.); 7.81 (d, 2H, J=8.3 Hz); 9.77 (s, 1H, CH=O).

MS (m/e, 70 eV): 444.19061 (M+, 100%), 426.18390 (M+ - H2O).

b) Production of the Compound According to the Invention:

4-[17β-Hydroxy-17α-(trifluoromethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde-(1E)-oxime (Compound No. 1):

549 mg of 4-[17β-hydroxy-17α-(trifluoromethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde is dissolved in 5 ml of pyridine, mixed with 83 mg of hydroxylamine hydrochloride and stirred for 1.5 hours at room temperature. Then, the solution is stirred into ice water. The precipitate is suctioned off, washed with water and dried. The crude product is purified by means of chromatography on silica gel (0.05–0.063 mm) with a hexane/ethyl acetate gradient. 493 mg of crude product is obtained, which is recrystallized from tert-butyl methyl ether/n-hexane.

Melting point: 163–167°C. While decomposing (tert-butyl methyl ether/n-hexane)

αD = +244° (CHCl3)

1H-NMR: [300 MHz, CDCl3, TMS]: 0.60 (s, 3H, H-18); 4.44 (d, 1H, J=7.1 Hz, H-11α); 5.80 (s, 1H, H-4); 7.20 (d, 2H, J=8.3 Hz, CH-arom.); 7.50 (d, 2H, J=8.3 Hz); 7.70 (s, 1H, NOH); 8.10 (s, 1H CH=N).

MS (m/e, 70 eV): 459.20001 (M+, 442.199931 (M+ - CH3O).

EXAMPLE 2

a) Production of the Starting Compound:

4-[17β-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde

20 g of 3,3-dimethoxy-11β-[4-(1,1-ethylenedioxy) methyl]phenyl]-5α-hydroxy-estr-9-en-17-one is suspended in 600 ml of diethyl ether and cooled to ~78°C. While being stirred. 48 g of pentafluoroethyl iodide is added, and then 76 ml of a 1.5 ml solution of methyllithium-lithium bromide complex in diethyl ether is slowly added in drops. It is stirred for 2 hours at ~78°C and then poured into 2 l of saturated sodium bicarbonate solution. Then, it is extracted with ethyl acetate, dried and concentrated by evaporation. The residue is taken up in 200 ml of 70% acetic acid and heated for 60 minutes to 60°C. It is allowed to cool and mixed with 400 ml of water, whereby the product precipitates. The precipitate is suctioned off, washed with water and boiled with tert-butyl methyl ether. 4-[17β-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde is obtained.

Melting point: 220–230°C (tert-butyl methyl ether)

1H-NMR (CDCl3): 0.58 (s, 3H, H-18); 4.52 (d, 1H, J=7.03 Hz, H-11α); 5.81 (s, 1H, H-4); 7.38 (d, 2H, J=7.81 Hz, CH-arom.); 7.81 (d, 2H, J=8.6 Hz); 9.96 (s, 1H, CH=O).

19F-NMR: 77.8 (3F,CF3), 119 (2F,CF2)

b) Production of the Compound According to the Invention:

4-[17β-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde-(1E)-oxime (Compound No. 4):

2.5 g of 4-[17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde is dissolved in 32 ml of pyridine and reacted with 450 mg of hydroxylamine-hydrochloride within 4 hours at room temperature. It is poured into ice water, the precipitate is suctioned off, dried and purified by means of chromatography. After recrystallization from acetone, 4-[17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde-(1E)-oxime is obtained.

Melting point: 220–230°C.

1H-NMR: 0.59 (s, 3H, H-18); 4.45 (d, 1H, J=6.6 Hz, H-11α); 5.80 (s, 1H, H-4); 7.20 (d, 2H, J=8.2 Hz,
EXAMPLE 3

4-(17β-Hydroxy-17α,1,1,2,2,2-pentafluoroethyl)-3-oxo-4,9-dien-11β-yl]-benzaldehyde-1-one (1-E)-(O-ethylamino) carbonyl-oxime (Compound No. 4)

1.4 g of 4-(17β-hydroxy-17α,1,1,2,2,2-pentafluoroethyl)-3-oxo-4,9-dien-11β-yl]-benzaldehyde-1-one (1-E)-(O-ethylamino) carbonyl-oxime is dissolved in 50 ml of toluene, mixed with 2.26 ml of triethylamine as well as 1.2 ml of methyl ascorbic acid and heated to 60°C. The mixture is stirred for 1.5 hours, cooled to 10°C C., mixed with 25 ml of aqueous ammonia solution as well as 100 ml of ethyl acetate and stirred for 30 minutes. After the phase separation, the organic phase is washed neutral with water, dried with sodium sulfate and concentrated by evaporation under vacuum. The residue is re-crystallized from ethyl acetate. 4-(17β-Hydroxy-17α,1,1,2,2,2-pentafluoroethyl)-3-oxo-4,9-dien-11β-yl]-benzaldehyde-1-one (1-E)-(O-ethylamino) carbonyl-oxime is obtained.

Melting point: 140–146°C (ethyl acetate)

H-NMR: 0.59 (s, 3H, H-18), 1.24 (t, 1H, J=7.2 Hz, CH3), 0.12 (d, J=6.8 Hz, 1H, H-11), 5.80 (s, 1H, H-4), 0.62 (t, 1H, J=5.7 Hz, —CH2—), 1.72 and 5.79 (2d, 2H, J=9 Hz, and CH-acrom each) 8.29 (2H, 1H, CH=N).

19F-NMR (386 MHz): 77.3 (3F, CF3), 119 (2F, CF2)

EXAMPLE 4

a) Production of the Starting Compound:

11β-{[4-(1,1-Ethyleneoxy)methyl]phenyl}-17α(1,1,2,2,2-pentafluoroethyl)-3,17β-trimethoxy-estr-9-en-5α-ol

620 mg of 3,3,3-dimethiophen-11β-{[4-(1,1-ethylenedi-2,2,2-pentafluoroethyl)methyl]-17α(1,1,2,2,2-pentafluoroethyl)-estr-9-ene-5α,17β-diol is dissolved in methanol and under argon cover gas in 5 ml of toluene. 232 mg of potassium-tert-butanolate is added in portions alternately with methyl iodide in toluene over 2 hours. After 3 hours, it is mixed with 20 ml of water, and the phases are separated. The aqueous phase is extracted again with toluene, the combined extracts are washed neutral and dried on sodium sulfate.

After concentration by evaporation, 662 mg of crude product is obtained as a foam, which is used without further purification in stage B.

H-NMR: [400 MHz, CDCl3, TMS]: 0.56 (s, 3H, H-18); 2.35 (s, 1H, OH), 3.20 and 3.22 (2s, 3H, and 2xOCH3 each), 3.33 (s, 3H, OCH3), 4.08 (m, 4H, ethylene ketals), 4.29 (d, 1H, J=7.2 Hz, H-11a), 4.62 (I, 1H, CH3), 5.74 (s, 1H, 5-OH), 7.23 (d, 2H, J=8.0 Hz, CH-acrom); 7.37 (d, 2H, J=8.0 Hz, arn. CH)

b) Stage B:

4-(17β-Methoxy-17α(1,1,2,2,2-pentafluoroethyl)-3-oxo-4,9-dien-11β-yl]-benzaldehyde

640 mg of 11β-{[4-(1,1-ethylenedi-2,2,2-pentafluoroethyl)ethyl]-17α(1,1,2,2,2-pentafluoroethyl)-3,17β-trimethoxy-estr-9-en-5α-ol is dissolved under argon cover gas in 10 ml of acetone, mixed with 300 mg of p-toluene sulfonic acid and stirred for 1 hour at room temperature. The reaction solution is stirred into 500 ml of ice water, whereby a product precipitates in a flocculent manner. It is neutralized with aqueous sodium bicarbonate solution, the precipitate is suctioned off, the filtrate is washed with water and dried. 411 mg of crude product, which is purified with the aid of preparative layer chromatography, is obtained.
acetic anhydride, mixed with 1.5 ml of water and 350 mg of p-toluene sulfonic acid and stirred for 1 hour at room temperature. It is diluted with water and extracted with methyl-ene chloride. The organic phase is washed neutral, dried and concentrated by evaporation. 663 mg of 4-[17β-hydroxy-17α-(1,1,1-trifluoroethyl)methyl]-3-oxoestr-4,9-dien-11β-yl]benzaldehyde is obtained as a foam. The crude product is purified by preparative layer chromatography.

Melting point: 100-103°C (ether)

**H-NMR: [400 MHz, CDCl₃, TMS]:** 0.53 (s, 3H, H-18); 3.45 and 3.91 (2m, 2xCH₂); 4.45 (d, 1H, J=7.2 Hz, H-11α); 5.81 (s, 1H, H-4); 7.37 (d, 2H, J=8.1 Hz, CH-arom.); 7.61 (d, 2H, J=8.1 Hz); 9.98 (s, 1H, NH=O).

b) Production of the Compound According to the Invention:

4-[17β-Hydroxy-17α-(1,1,2,2,3,3,3-heptafluoropropyl)-3-oxoestr-4,9-dien-11β-yl]-benzaldehyde-(1E)-oxime (Compound No. 22)

For the production of the title compound, 340 mg of 4-[17β-hydroxy-17α-(1,1,2,2,3,3,3-heptafluoropropyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde according to Example 2 is reacted. 326 mg of crude product is obtained. The crude product is purified by preparative layer chromatography on silica gel PF₂₅₄ nm.

Melting point: 132-136°C (ether)

**H-NMR (400 MHz, CDCl₃, δ in ppm, TMS):** 0.53 (s, 3H, H-18); 3.45 and 3.80 (m, 2H and CH₂ each); 4.39 (d, J=6.8 Hz, H-11); 5.80 (s, 1H, H-4); 7.20 and 7.49 (2d, 2H, J=8.4 Hz, and CH-arom. each); 7.60 (s, 1H, OH); 8.11 (s, 1H, NH=)

**F-NMR (386 MHz):** 58.4 (s), 78.3 (s), 110.7 (d) and 113.8 (d)

### EXAMPLE 7

a) Production of the Starting Compound:

4-[17β-Hydroxy-17α-(1,1,2,2,3,3,3-heptafluoropropyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde

965 mg of 3,3-dimethoxy-11β-[4-(1,1-ethylenedioxy) methyl]phenyl]-5α-hydroxy-estr-9-ene-17-one is dissolved in 35 ml of absolute THF, mixed with 1.0 g of molecular sieve 3 Å and stirred for 30 minutes under argon. It is cooled to 0°C, 0.5 ml of 1,1,2,2,3,3,3-heptafluoropropyltrimethylsilane is added, stirred for 10 more minutes, and then 55 mg of tetrabutylammonium fluoride is added. After 10 minutes at 0°C, the reaction solution is decomposed by adding 10 ml of 1N HCl. It is allowed to reach room temperature, stirred for 2 more hours, cooled again to 0°C, and another 0.5 ml of 1,1,2,2,3,3,3-heptafluoropropyltrimethylsilane is added. After 15 minutes, the solution is hydrolyzed by adding 15 ml of 1N HCl. After another 30 minutes, 100 ml of saturated ammonium chloride solution is added, and the solution is extracted with ethyl acetate. The organic phase is washed neutral, dried on sodium sulfate, the organic phase is filtered off and concentrated by evaporation under vacuum. The brown crude product (924 mg) is purified by means of chromatography on silica gel with ethyl acetate/n-hexane 1:2. Recrystallization from acetone/n-hexane yields 485 mg of 4-[17β-hydroxy-17α-(1,1,2,2,3,3,3-heptafluoropropyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde.

b) Production of the Compound According to the Invention:

4-[17β-Hydroxy-17α-(1,1,2,2,3,3,3-heptafluoropropyl)-3-oxoestr-4,9-dien-11β-yl]-benzaldehyde-(1E)-oxime (Compound No. 10)

The title compound is produced according to Example 2 from 4-[17β-hydroxy-17α-(1,1,2,2,3,3,3-heptafluoropropyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde by reaction with hydroxylamine hydrochloride in pyridine.

Melting point 170-175°C.

H-NMR: 0.59 (s, 3H, H-18); 4.45 (d, 1H, J=6.6 Hz, H-11α); 5.80 (s, 1H, H-4); 7.20 (d, 2H, J=8.2 Hz, CH-arom.); 7.48 (d, 2H, J=8.2 Hz); 8.10 (s, 1H, CH=NO).

As one skilled in the art can easily discern, any changes and modifications to the preferred embodiments of the invention shown here are included in the scope of protection of the attached claims. This also means that any combinations of features of this invention are included in the disclosure content.

What is claimed is:

1. 17α-Fluoroalkyl-11β-benzaldoxime steroids with general formula I

![Chemical structure](attachment:chemical_structure.png)

in which R₁ stands for hydrogen, C₃- to C₅-alkyl, COR₂, COOR₃, COSR₄ or CONHR₅, in which R₂ is C₁- to C₄-alkyl or unsubstituted or substituted arenyl and in which R₃ is hydrogen, C₃- to C₅-alkyl or unsubstituted or substituted aryl, and R₄ stands for hydrogen, C₁- to C₄-alkyl or C₁- to C₄-aclyl, and R₅ stands for a C₅F₂₅₄ group, in which n=1,2 or 3, or for a CH₂O(CH₂)ₙC₅F₂₅₄ group, in which m=0 or 1 and n=1,2 or 3, as well as their pharmaceutically compatible salts.

2. 17α-Fluoroalkyl-11β-benzaldoxime steroids according to claim 1, characterized in that R₁ stands for hydrogen, methyl, formyl, acetyl, propionyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, ethylthiocarbonyl, ethylaminocarbonyl or substituted phenylaminocarbonyl.

3. 17α-Fluoroalkyl-11β-benzaldoxime steroids according to claim 2, wherein the substituted phenylaminocarbonyl radical is substituted with a C₁- to C₆-perfluoralkyl radical.

4. 17α-Fluoroalkyl-11β-benzaldoxime steroids according to claim 1, wherein R₂ stands for hydrogen, methyl or acetyl.

5. 17α-Fluoroalkyl-11β-benzaldoxime steroids according to claim 1, wherein R₃ stands for 1,1,1-trifluoromethyl, 1,1,2,2,2-pentafluoroethyl, 1,1,2,2,3,3,3-heptafluoropropyl or 1,1,1-trifluoroethylmethyl.

6. 17α-Fluoroalkyl-11β-benzaldoxime steroids according to claim 1, namely

1) 4-[17α-Hydroxy-17α-(1,1,1-trifluoromethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde-(1E)-oxime

2) 4-[17α-Hydroxy-17α-(1,1,1-trifluoromethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde-(1Z)-oxime

3) 4-[17α-Hydroxy-17α-(1,1,1-trifluoromethyl)-3-oxoestr-4,9-dien-11β-yl]benzaldehyde-(1E)-O-ethyl[bisoxime]
13

4-[17\beta-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-oxime
5
4-[17\beta-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
acetyl oxide
6
4-[17\beta-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethyl amino carboxyl) oxide
7
4-[17\beta-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethythio carboxyl) oxide
8
4-[17\alpha-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethoxy carboxyl) oxide
9
4-[17\beta-Hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(methoxy carboxyl) oxide
10
4-[17\beta-Hydroxy-17α-(1,1,2,2,3,3,3-heptafluoropropyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-oxime
11
4-[17\beta-Methoxy-17α-(1,1,1-trifluoromethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-oxime
12
4-[17\beta-Methoxy-17α-(1,1,1-trifluoromethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethylamino carboxyl) oxide
13
4-[17\beta-Methoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-oxime
14
4-[17\beta-Methoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
acetyl oxide
15
4-[17\beta-Methoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethylamino carboxyl) oxide
16
4-[17\beta-Methoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
[(4'-trifluoro-methyl oxy) benzyl amino carboxyl] oxide
17
4-[17\beta-Methoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethoxy carboxyl) oxide
18
4-[17\beta-Methoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethyl carboxyl) oxide
19
4-[17\beta-Acetoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-O-
(ethylamino carboxyl) oxide
20
4-[17\beta-Acetoxy-17α-(1,1,2,2,2-pentafluoroethyl)-3-
oxoestra-4,9-dien-11β-yl]benzaldehyde-1(E)-oxime
21

14

4-[17\beta-Hydroxy-17α-[(1,1,1-trifluoromethoxy)
methyl]-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1
(E)-oxime.

7. Process for the production of 17α-fluoroalkylated 11β-
benzoaldehyde oximes with general formula I

OR3

in which radicals R1, R2 and R3 have the meanings that are
indicated in claim 1, wherein an 11β-benzaldehyde with
the meaning of II

OR2

is reacted with a salt of a hydroxylamine in a basic solution,
so that a 17α-fluoroalkyl-11β-benzoaldehyde steroid is
produced, in which R1 is hydrogen, and this compound
optionally is esterified, etherified or converted into a cor-
responding carbamate, carboxylic acid derivative or thio-
carboxylic acid derivative.

8. Process according to claim 7, wherein the salt of the
hydroxylamine is a hydrochloride or hydroxysulfate.

9. Process according to claim 7, wherein the basic solvent
is pyridine.

10. Pharmaceutical preparation that contains at least one
17α-fluoroalkyl-11β-benzoaldehyde steroid with the general
formula I according to claim 1 as well as at least one
pharmacologically compatible vehicle.

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